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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,816	11/04/2003	Zuoshang Xu	UMY-038	9864

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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,816	XU ET AL.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 28-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 28-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/17/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

Applicant's arguments with respect to the claimed invention have been considered but are moot in view of the new ground(s) of rejection below. The declaration filed by the inventors under 37 CFR 1.131 on 9/17/07 has been considered and provides sufficient evidence to remove the Davidson et al reference as prior art. The new grounds of rejection below are in response to and caused by applicants actions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 and 28-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreutzer et al [US 2005/0074757 A1], Elbashir [The EMBO Journal Vol. 20(23), 2001, cited by applicant as C15 in IDS filed 9/17/07], Klug et al [European

Journal of Physiology, Vol. 441 (6 Suppl): R205, 2001], Brown et al [WO 94/19493], Siddique et al [Neurology Vol. 47(suppl 2): S27-S35, 1996], and Kunst et al [Nature Genetics Vol. 15: 91-94, 01/15/96].

The instant invention is drawn to the inhibition of a targeted specified allele in a cell via siRNA. The invention is more specifically drawn to dominant gain of function alleles of specified diseases and to specified alleles and to the use of specific siRNA and shRNA targeted to specific ALS alleles. The invention is clearly set forth in the claims and no interpretation is required to apply the prior art.

Kreutzer et al have taught the use of dsRNA to target mutant genes. At paragraph [0006] it is taught that it is desirable to inhibit a mutant gene comprising a point mutation without also inhibiting the expression of the normal, nonmutated gene. It is taught that compounds that have such a capacity would be useful for treating genetic diseases and disorders caused by the expression of a gene having a minor mutation, such as a single or multiple-base mismatch. In paragraph [0015] it has been taught that the use of dsRNA targeted to a mutant allele allows for the inhibition of the mutant allele while allowing the expression of the wild-type allele. In paragraph [0023] it is taught where the mismatch may be placed within the dsRNA. In paragraphs [0060]-[0063] it has been taught that any disease associated target genes having point mutations can be targeted. Kreutzer et al have taught to inhibit disease associated mutants that contain point mutations such that the mutant is inhibited while the wild-type is not. Kreutzer et al have not specifically pointed to a specific subgenus of target genes that have point mutations that are dominant gain of function mutants. The subgenus and

species within are, however within the scope of gene targets taught by Kreutzer and the prior art below also shows that such targets are obvious targets. The Kreutzer reference also does not teach the specific position of mismatch locations or specific targets recited in the claims. The prior art below provides such teachings.

Elbashir et al have taught position effects of mismatches in siRNA function. At page 6878 it is taught, for example that target recognition is extremely specific, as evan single nucleotide mismatches between the siRNA duplex and the target mRNA abolish interference. And assert that this provide a rational basis for the design of siRNAs. At page 6885 it has been taught that "[n]ucleotides in the center of the siRNA, located opposite to the target RNA cleavage site, are important specificity determinants and even single nucleotide changes reduce RNAi to undetectable levels. This suggests that siRNA duplexes may be able to discriminate mutant or polymorphic alleles in gene targeting experiments, which may become an important feature for future therapeutic developments."

Brown et al have taught the involvement of SOD1 and in particular specific mutations in SOD1 that lead to dominant gain of function ALS (see page 28, for example). At pages 10, 31, 53, and claims 43-45 and 47, for example) it is taught to inhibit mutant SOD1 via antisense. In Tables 3A and 3C, the specific mutations targeted by the instant invention are disclosed [G256C and G281C which correspond to G85Arg and G93A].

Klug et al have taught the targeting of the most common SOD1 mutant gain of function allele G93A with antisense. It was shown the selective inhibition of the mutant allele and uptake of antisense in the brain.

Siddique et al have disclosed SOD1 mutations associated with ALS (see Table, for example).

Kunst et al have also shown that the specific mutant alleles for SOD1 associated ALS were well known at the time of invention (see Figure 1, for example.

The prior art has therefore shown that SOD1 dominant gain of function mutants are causative for ALS. The prior art has shown the targeted inhibition of specific SOD1 alleles via antisense.

The prior art has taught that siRNA can be used to specifically target a desired allele of a gene. The prior art has also taught to specifically inhibit dominant gain of function alleles, including the specific allele of SOD1 recited in the instant claims.

The prior art has shown that mutations associated with ALS (SOD1 have been known for some time before the instant invention. The prior art has also taught to target the mutant alleles of SOD1 selectively over the wt. Since the prior art has also asserted the usefulness of siRNA for treating ALS it would have been obvious to use them since the prior art has shown that such targeting was successful using antisense. Since the sequence of SOD1 and more importantly since the specific mutant sequences were known and the art clearly suggest targeting them, the siRNA sequences of the instant invention are merely optimizations at best.

The invention as a whole would therefore have been *prima facie* obvious at the time the invention was made.

Claims 41-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreutzer et al [US 2005/0074757 A1], Elbashir [The EMBO Journal Vol. 20(23), 2001, cited by applicant as C15 in IDS filed 9/17/07], Klug et al [European Journal of Physiology, Vol. 441 (6 Suppl): R205, 2001], Brown et al [WO 94/19493], Siddique et al [Neurology Vol. 47(suppl 2): S27-S35, 1996], and Kunst et al [Nature Genetics Vol. 15: 91-94, 01/15/96]. as applied to claims 1-12 and 28-40 above, and further in view of Brummelkamp et al [Science Express, 21 March 2002, cited by applicant as C6 on IDS filed 9/17/07.

The added limitations addressed herein are the expression of siRNAs of the invention from a vector and such that the siRNA are first expressed as an shRNA and the use of recited Pol III promoter.

Brummelkamp et al have taught the use of pSuper vectors that utilize pol III promoter to express siRNA as shRNA for the benefit of stable expression of siRNA to mediate persistent suppression of a target gene allowing for the analysis of loss of function phenotypes that developed over an extended period of time. One in the art would clearly have recognized this extended expression benefit in the treatment of disease since one in the art would clearly recognize that the successful treatment of a

genetic disease would benefit from administration of a drug that is stably expressed that over that of transient administration, for example. The prior art has taught the use of Pol III promoters such as the recited U6 promoter has been widely used, as the HI exemplified in Brummelkamp. Those in the art are well aware of the benefits of using Pol III promoters to express short RNAs.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claim Objections

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 5 requires that the siRNA is targeted to the gain of function mutation. The context of the claims from which this claim depends require that this limitation be met prior to its recitation in the subject claim. If applicant believes that this claim does indeed further limit the invention of the claims from which it depends applicant should provide an explanation.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry
Primary Examiner
Art Unit 1635

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